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Research article

"Healing effect of homeopathic drug Theranekron in an alkaline-induced corneal injury model in rats"

N.F. Karakuyu [a,*], M.N. Kaya [b], G. Usta Sofu [c], E. Sarman [d]

[a] Department of Pharmacology, Faculty of Pharmacy, Suleyman Demirel University, Isparta, Turkey
[b] Undergraduate Student, Faculty of Pharmacy, Suleyman Demirel University, Isparta, Turkey
[c] Department of Ophthalmology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey
[d] Department of Histology and Embryology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

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ABSTRACT

Corneal injuries, particularly those caused by alkaline substances, are challenging to treat and can lead to severe complications such as inflammation, ulceration, and blindness. Current treatments, including lavage, antibiotics, and steroids, often fail to provide rapid or complete recovery. Theranekron, a homeopathic preparation derived from the venom of the Tarantula cubensis spider, has shown anti-inflammatory and wound-healing properties in veterinary medicine. This study aimed to investigate Theranekron's potential in treating corneal damage in a rat model. Thirty-two rats were divided into four groups: damage, damage + dexamethasone, damage + ocular Theranekron, and damage + subcutaneous Theranekron. Corneal damage was induced using silver/potassium nitrate sticks, and treatments were administered for seven days. Clinical, histopathological, and immunohistochemical evaluations were conducted to assess inflammation, neovascularization, and tissue repair. Rats treated with Theranekron (both ocular and subcutaneous) showed significant reductions in inflammation, edema, and neovascularization compared to the untreated and dexamethasone groups. Immunohistochemical analysis revealed lower expression of inflammatory markers (TNF-α, NF-κB-p65) and VEGF in Theranekron-treated groups. Theranekron exhibited significant potential in promoting corneal healing by reducing inflammation and inhibiting neovascularization. Its effectiveness exceeds dexamethasone's, making it a promising alternative for treating corneal injuries. Further research is needed to explore its application in human ocular medicine and to optimize dosing and administration methods.

1. Introduction

Corneal injuries are a difficult ocular condition to treat, which is frequently seen in the clinic and can lead to serious consequences such as blindness (Yi and Zou, 2019). Injuries with alkaline substances can cause more serious consequences than injuries with acidic substances. This is because acidic substances denature the proteins in the cornea and form clots, preventing the chemical from penetrating. On the other hand, alkalis destroy proteoglycans and collagens in the cornea, causing the chemical to penetrate more (Fish and Davidson, 2010). As penetration increases in alkaline substances, complications can reach more serious dimensions (Barouch and Colby, 2008). Examples of complications include inflammation, ulceration, perforation, tissue damage, and necrosis. In the treatment of alkaline chemical injuries in the clinic, lavage applications are performed to remove the chemical. Then, some antibiotics, steroid or nonsteroidal drugs (especially dexamethasone), or surgical treatment methods are applied. However, these treatments do not provide rapid treatment or complete recovery (Ke et al., 2015).

Homeopathy is a medical system based on the principle of similarity, unlike allopathy, which is used today as modern medicine. In a report prepared by the World Health Organization, homeopathy is accepted as the most widely used and most frequently preferred traditional treatment application (WHO, 2009). Hahnemann, known as the founder of homeopathy, explains homeopathic treatment as "A weaker dynamic effect is eliminated by a similar and stronger effect" (Hahnemann, 2009). Theranekron is a homeopathic preparation frequently used in veterinary medicine. It is obtained by diluting the venom of the tarantula cubensis spider 10^6 times in alcohol. It is known to have

* Corresponding author. Suleyman Demirel University, Faculty of Pharmacy, Department of Pharmacology, Isparta, Turkey.
E-mail addresses: fatihkarakuyu@sdu.edu.tr (N.F. Karakuyu), mervenure024@gmail.com (M.N. Kaya), gulsahusta@sdu.edu.tr (G. Usta Sofu), emine.sarman@afsu.edu.tr (E. Sarman).

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anti-inflammatory, anti-necrotic, wound healing effects. The digestive enzymes in the spider's venom can cause serious inflammation, arachnoidism, kidney damage, tissue damage, and even necrosis (Saez et al., 2010). However, it is also frequently used as a drug in veterinary medicine by sc route in the treatment of these indications. In addition, there are studies in literature showing that Theranekron can be used in the treatment of many new diseases (Güven et al., 2022; Kizilay et al., 2019; Savran et al., 2022).

It is difficult to obtain rapid and complete results from the treatments used to heal corneal burn lesions mentioned above. Therefore, new treatment methods are the subject of research. In this study, we have discussed Theranekron, a homeopathic preparation obtained from the venom of the Tarantula cubensis spider, licensed for veterinary wound healing treatment. As a result of our literature review, it was found that Theranekron was used for wound healing in different tissues, that studies were conducted and that these studies yielded successful results. However, we discovered that this healing effect was not studied for the corneal damage model. This study aimed to investigate the healing effect of Theranekron in an experimentally induced corneal damage model in rats.

2. Materials and method

2.1. Ethical approval

The study was carried out with the approval of the Suleyman Demirel University Animal Research Ethics Committee (Ethics No: 26.03.2024–04/268). All experiments were performed in conformity with adhered to ARVO's regulations for using animals in ophthalmic and vision research.

2.2. Experimental design

Thirty-two 12-week-old female rats obtained from Suleyman Demirel University Experimental Animals Laboratory were divided into 4 groups with 8 animals in each group.

To create a corneal damage model, all rats' central regions of the left eye corneas were cauterised with Silver/Potassium Nitrate sticks (75 % silver nitrate, 25 % potassium nitrate; Medbar, Izmir, Turkey) (Claros-Chacaltana et al., 2017). In order to standardise the size of the burn, cauterization was performed by the same investigator for 15 s to create a 2 mm diameter chemical burn. The burn was photographed. Right eyes were considered as control. The eyes of the rats were then washed with 10 mL of sterile saline (sf) (Polifleks 0.9 % isotonic sodium chloride, Polifarma, Istanbul, Turkey) drawn into a sterile syringe to wash and clean the silver nitrate remaining on the tissue surface. An eye drop of moxifloxacin (Moxai, Abdi İbrahim, Turkey) was administered to minimise the risk of infection. Fluorescein test was applied to the left eyes of both rats to check whether the damage occurred. After the corneal burn was created and the degree of damage was determined, drugs were administered to each group for 7 days as planned as follows:

Group 1 (Damage): Saline was administered one drop (0.05 ml) twice a day for 7 days to rats with left eye damage.
Group 2 (Damage + Dexamethasone): Eye drops containing dexamethasone (Onadron Simple, İbrahim Etem Menarini Group, Turkey) were administered one drop (0.05 ml) twice a day for 7 days to rats with left eye damage.
Group 3 (Damage + Topical Theranekron): Theranekron (Theranekron® D6, Richter Pharma, Wels, Austria) was administered one drop (0.05 ml) twice daily for 7 days to rats with left eye damage.
Group 4 (Damage + Sc. Theranekron): A single dose of 0.2 ml subcutaneous Theranekron was administered to the dorsal regions of rats immediately after corneal injury, and no further treatment was performed for seven days (Savran et al., 2022). No local reaction was observed at the injection site.

Twenty-four hours after the last drug administration (8th day), rats were brought to the laboratory for macroscopic evaluation. To put the rats under general anaesthesia, a mixture of ketamine (90 mg/kg) and xylazine (8–10 mg/kg) was administered intraperitoneally. The ketamine and xylazine were supplied by Doğa İlaç in Turkey under the brand names Keta-Kontrol and Control 10 %, respectively. The eyes were then examined under a light microscope. The extent of the residual damage in the eyes was determined, and the degree of recovery was evaluated by applying the Fluorescein test. The eyes of the rats were removed and stored in formaldehyde for further analyses. After the removal of the eyes, it was checked that the animals were under general anaesthesia, and euthanasia was performed by cervical dislocation.

2.3. Clinical evaluation

Slit-lamp examination was performed immediately after burn induction and seven days later to observe and record the inflammation of rat ocular surface. The inflammatory index score was calculated as follows: ciliary hyperemia (0 = none; 1 = less than 1 mm; 2 = 1 and 2 mm; and 3 = more than 2 mm); central corneal edema (0 = none; 1 = iris details can be seen; 2 = the details of the iris are unclear, but the pupil is visible; and 3 = the pupil is indistinct); and peripheral corneal edema (0 = none; 1 = there are visible iris details; 2 = no iris details visible; and 3 = no visible iris) (Mu et al., 2022). The clinical evaluation score was determined by summing up all these scores.

2.4. Histopathologic examinations

The tissues taken from each group were fixed in 10 % neutral buffered formaldehyde solution, washed overnight under running water, subjected to routine histological follow-up series (50 %, 60 %, 70 %, 70 %, 80 %, 96 %, 100 %), polished in xylol and embedded in paraffin blocks and 5μ thick sections were taken from these blocks. The sections were subjected to Haematoxylin-Eosin (HE) staining; After being kept in an oven at 60 °C for 60 min, they were made transparent in xylol, then passed through 100 %, 96 %, 90 %, 70 % alcohols and stained in Harris Haematoxylin for 3 min, immersed in 1 % acid + alcohol mixture and removed, washed in running water for 1 min, kept in Eosin for 2 min, passed through 70 %, 80 %, 96 %, 100 % alcohols, taken in xylol, covered with Entellan and made ready for examination (Candan et al., 2024). Inflammation and vascularization were evaluated in these sections; the amount of corneal inflammation was graded from 0 to 3 (0: 0–10 cells/field, 1: 11–30 cells/field, 2: 31–50 cells/field, 3: more than 50 cells/field) (Cheng et al., 2012). For vascularization and inflammation evaluations, vessels and inflammatory cells were counted and scored in six different image areas under ×40 objective magnification (Doğan et al., 2019).

2.5. Immunohistochemical examinations

Paraffin blocks prepared for histological analyses were deparaffinized after 5μ thick sections were taken. After 5 min treatment with H2O2 (TA-060-HP, Lab Vision Corporation, USA) and Ultra V Block (TA-125-UB, Thermo Scientific, UK) solution, the sections were incubated with nuclear factor kappa-light-chain-enhancer of activated B cells p65 (NF-κB-p65) (E-AB-32233, Elabscience, USA), tumor necrosis factor-alpha (TNF-α) (sc-52746, Santa Cruz, USA) and vascular endothelial growth factor (VEGF) (sc-57496, Santa-Cruz, USA) for 60 min. Incubated with secondary antibody (Biotinylated Goat Anti-Polyvalent TP-125-BN, Thermo Scientific, UK) and Strepavidin HRP (Horse radish peroxidase) (TS-125-HR, Thermo Scientific, UK) for 30 min at room temperature. After DAB (3,3′-diaminobenzidine) (TA-125 HD, Thermo Scientific, UK) solution, tissues were counterstained with Mayer's haematoxylin and covered with entellan. All preparations were evaluated and photographed using an Eclipse E−600 Nikon, Japan photomicroscope and image analysis system (NIS Elements Nikon, Japan)

(Sarman et al., 2023). The intensity of immunostaining was scored semi-quantitatively as (0, -) negative staining, (1, +) focal and weak staining, (2, +++) diffuse and weak staining and (3, ++++) intense and strong staining.

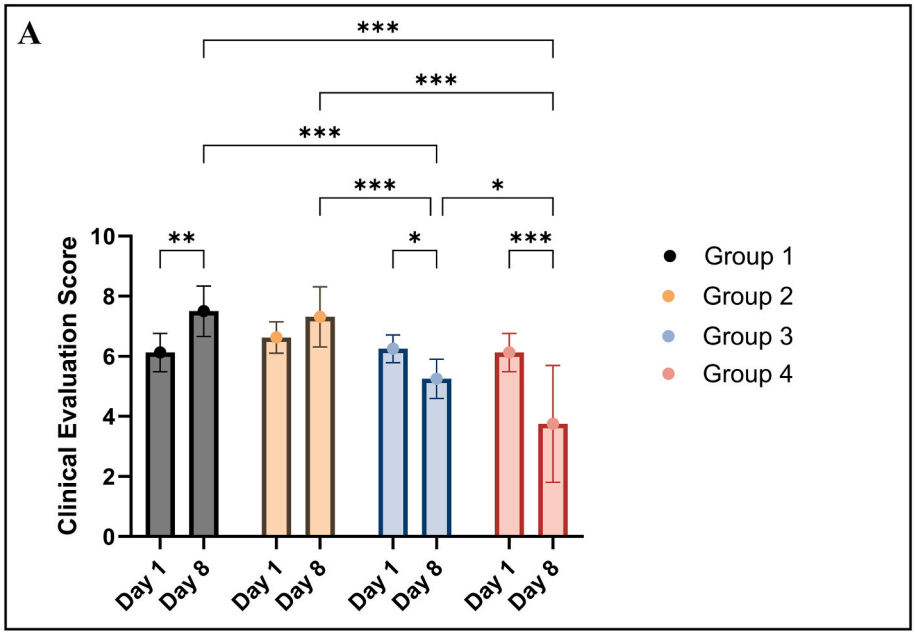
2.6. Statistical analysis

Statistical analysis of clinical, histopathological, and immunohistochemical evaluation results between groups was performed with one-way ANOVA and two-way ANOVA Tukey tests by using Graphpad Prism (v10.1.0) program. $p < 0.05$ was considered significant.

3. Results

3.1. Clinical evaluation results

At the beginning of the experiment (after cauterization), the left eyes of the animals in all groups were similarly highly damaged. Comparing the clinical scores of the left eyes at the end of the experiment, necrosis, intense inflammation, and edema were observed in the left eyes of animals in Group 1. Necrosis was observed in the left eyes of all animals in Group 2, and some animals had perforated eyes. No necrosis or perforation was observed in the left eyes of all animals in Groups 3 and 4, and inflammation and edema were less than in the other groups. Especially, the left eyes of Group 4 were found to be significantly better than in the other groups. The right eyes, which were the control group, were not included in the clinical evaluation because no negative changes were observed.



B

Groups:	Group 1	Group 2	Group 3	Group 4
Day 1	6,12 ± 0,64	6,62 ± 0,51	6,25 ± 0,46	6,12 ± 0,64
Day 8	7,50 ± 0,83	7,31 ± 0,99	5,25 ± 0,65	3,75 ± 1,94

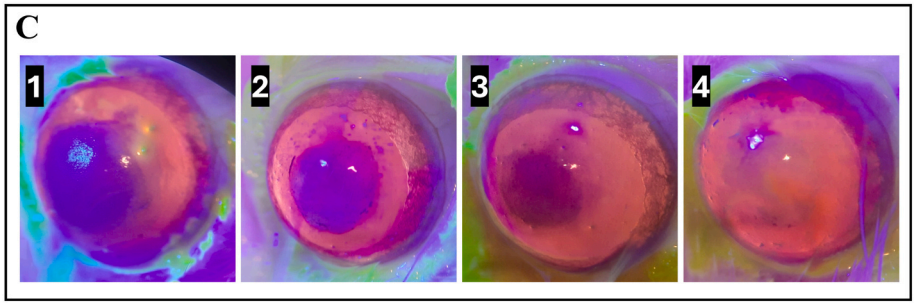


Fig. 1. Clinical evaluation results
A- Statistical analysis results. Statistical analysis was performed with two-way ANOVA Tukey test "*" represents $p < 0.05$, "**" represents $p < 0.005$, "***" represents $p \leq 0.001$.
B- Clinical evaluation scores. Values are presented as means ± standard deviation.
C- Representative eye photographs at the end of the experiment. 1: Group 1 (Damage), 2: Group 2 (Damage + Dexamethasone), 3: Group 3 (Damage + Theranekron), 4: Group 4 (Damage + Sc. Theranekron).

When the beginning and end of the experiment were compared, it was observed that the clinical evaluation scores in the eyes of Groups 1 and 2 increased. A significant decrease was observed in the clinical evaluation score of the left eyes of Groups 3 and 4. This decrease was most significant in Group 4 ($p < 0.0001$) (Fig. 1).

3.2. Histopathologic examinations results

In the corneal injury model due to chemical burn, corneal inflammation and vascularization were evaluated with light microscopy after treatment in the subjects. In the control group, the corneal epithelium, Bowman layer, stroma, Descement membrane, and corneal endothelium had a normal appearance. In Group 1, congestion, inflammation, and the number of vessels were observed to increase in the burn periphery. In Group 2, it was determined that the areas of inflammation and congestion were less compared to Group 1. In Group 3 and Group 4, it was determined that inflammation and the number of vessels were significantly reduced compared to Group 1 and Group 2 (Figs. 2 and 3).

3.3. Immunohistochemical examinations results

TNF-α, NF-κB-p65, and VEGF antibodies were studied to determine inflammation and neovascularization. TNF-α, NF-κB-p65, and VEGF immunoreactivity was not observed in the tissues of the control group. High-intensity TNF-α, NF-κB-p65, and VEGF immunoreactivity was detected in Group 1.

The immunoreactivity observed for TNF-α in Group 2 was significantly lower than in Group 1 ($p < 0.05$). Similarly, immunoreactivity was significantly lower in Groups 3 and 4 than in Group 1 ($p < 0.005$, for both). For NF-κB-p65 and VEGF, the immunostaining score of Group 2 was found to be similar to Group 1, but significantly higher than in Groups 3 and 4 ($p \leq 0.001$, for all). The immunostaining scores of Groups 3 and 4 were also significantly lower than Group 1 ($p \leq 0.001$, for all) (Figs. 3 and 4).

4. Discussion

When alkaline substances such as bleach and chalk come into contact with the eye, they quickly penetrate the tissue and cause damage. In severe cases, corneal damage or infection may even require surgical intervention. In emergency treatment, it is critical to wash the eye, then regulate the eye pH and use anti-inflammatory/antibiotic drops. Currently, the efficacy of various anti-inflammatory substances is being investigated for the prevention of inflammation due to alkali burn (Liu et al., 2023).

This study examines the healing effects of a homeopathic preparation, Theranekron, on a corneal injury model induced by chemical burns in rats. In order to perform the study, it is firstly necessary to establish a chemical burn model in rats. The fact that the clinical evaluation scores of the first day were similar for all groups indicates that the damage model was created in a standardized manner. The fact that the eighth-day clinical assessment scores were significantly higher in Group 1 compared to the first-day scores indicates that corneal healing did not occur and even worsened. The high score in Group 2 on the eighth-day can be interpreted as the healing process has started but is not reflected in the clinic. The fact that the eighth-day scores of Groups 3 and 4 were lower than the first-day scores indicates that the textural healing process started in these groups.

According to both clinical evaluation and histopathological examination results, inflammation findings in group 1, which are similar to the literature, indicate that the damage model was successfully created (Yılmaz et al., 2019). The significant decrease in histological inflammation findings in Groups 2, 3 and 4 compared to Group 1 suggests that the drugs used in the treatment (dexamethasone, Theranekron) were effective. In addition, the fact that the inflammation findings in Groups 3 and 4 were significantly lower than Group 2 suggested that Theranekron caused more anti-inflammatory response than dexamethasone.

The literature on the role of homeopathic remedies such as Theranekron in corneal healing is limited. However, some studies support its

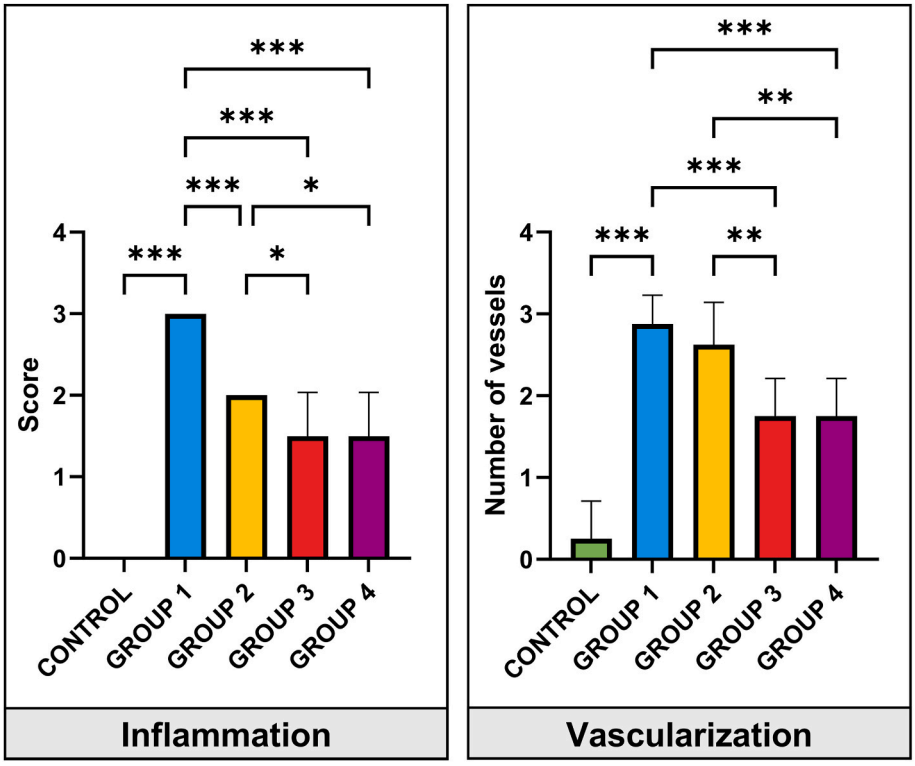


Fig. 2. Histopathologic scores among groups Statistical analysis was performed with one-way ANOVA Tukey test "*" represents $p < 0.05$, "**" represents $p < 0.005$, "***" represents $p \leq 0.001$. Group 1: Damage, Group 2: Damage + Dexamethasone, Group 3: Damage + Theranekron, Group 4: Damage + Sc. Theranekron.

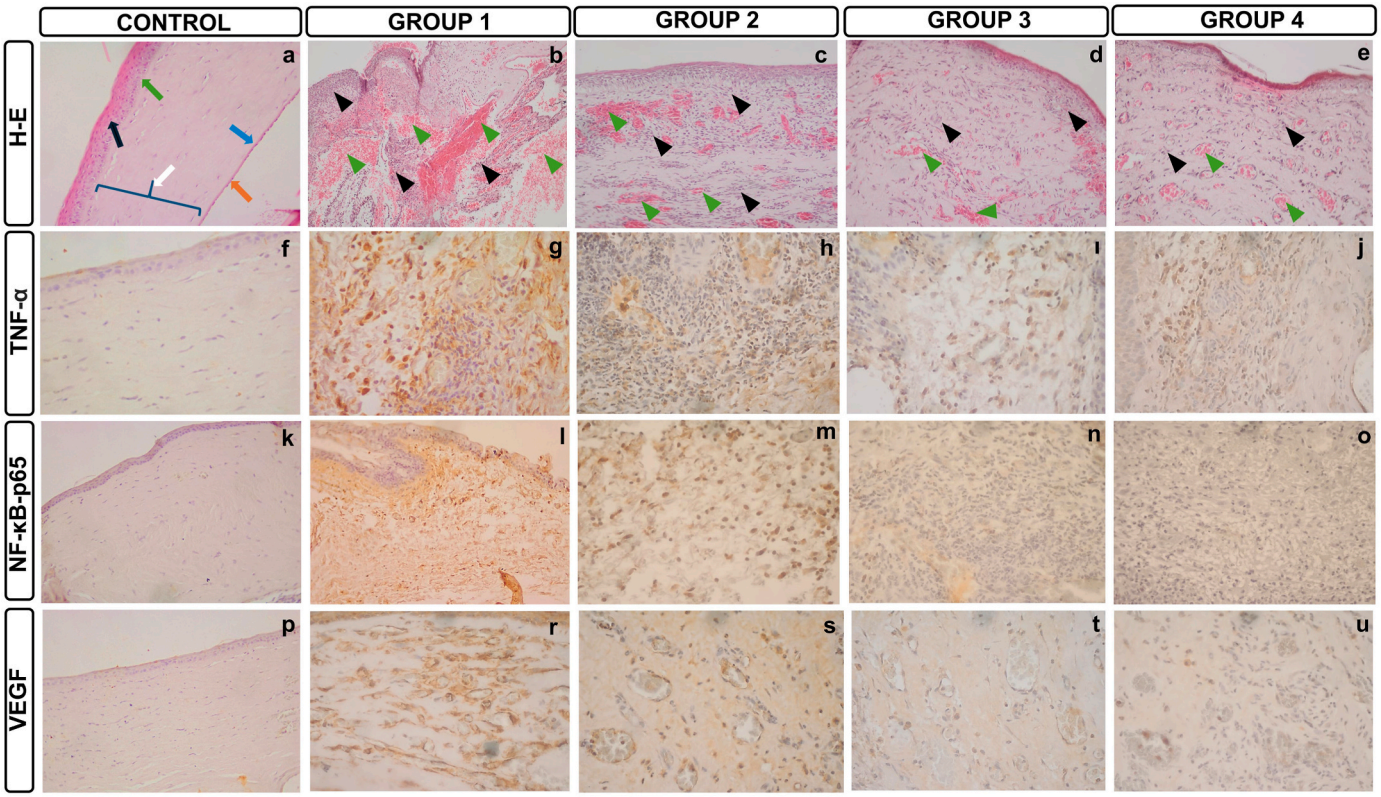


Fig. 3. Histopathologic and immunohistochemical staining results
Corneal epithelium (black arrow), Bowman's layer (green arrow), stroma (white arrow), descement membrane (blue arrow), and corneal endothelium (orange arrow) appear normal in the control group (a). In Group 1 (Damage Group), increased congestion (green arrowhead) and inflammation (black arrowhead) were observed in the periphery of the burn (b). In Group 2 (Damage + Dexamethasone), the areas of inflammation (black arrowhead) and congestion (green arrowhead) were less than in Group 1 (c). In Group 3 (Damage + Theranekron) and Group 4 (Damage + Sc. Theranekron), inflammation (black arrowhead) and congestion areas were significantly reduced, and vascularization (green arrowhead) was increased (d,e).
TNF-α, NF-κB-p65, VEGF immunoreactivity was not observed in the tissues of the control group (f, k, p). In Group 1, TNF-α, NF-κB-p65, and VEGF immunoreactivity were detected at +3 (g, l, r). In Group 2, immunopositive areas with a severity of +2 were visible (h, m, s). In Group 3 and Group 4, TNF-α and NF-κB-p65 immunoreactivities decreased compared to Group 1 and were found to be +2 (i, j, n, o); VEGF immunoreactivity was found to be +1 (t, u).
a, b, c, d, e, f, k, p (x20; scale bar, 100 μm), g, h, i, j, l, m, n, o, r, s, t, u (x40; scale bar, 50 μm), Group 1: Damage, Group 2: Damage + Dexamethasone, Group 3: Damage + Theranekron, Group 4: Damage + Sc. Theranekron, H–E: Haematoxylin-Eosin, TNF—α: Tumor necrosis factor alpha, NF-κB-p65: Nuclear factor kappa-light-chain-enhancer of activated B cells p65, VEGF: Vascular endothelial growth factor. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

anti-inflammatory effects. For example, in the study by Savran et al., Theranekron was shown to reduce the expression of pro-inflammatory cytokines by suppressing the NF-κB signalling pathway in an acetic acid (AA)-induced colitis model (Savran et al., 2022). In another rat study, intravesical Theranekron demonstrated anti-inflammatory activity by reducing levels of inflammatory parameters such as IL-6 and TNF-alpha in bladder tissue (Abdullah et al., 2023). Theranekron protected rat ovaries against ischaemia-reperfusion injury by reducing the expression of inflammatory markers such as IL-1β, IL-6 and TNF-alpha in the study by Paksoy et al. (2025). In this study, Theranekron reduced the expression of TNF-α and NF-κB-p65 in ocular tissues as shown by immunohistochemical staining, consistent with these studies. Considering the connection between NF-κB-p65 and chronic inflammation, it can be said that Theranekron can reduce inflammation in both acute and chronic phases (Giridharan and Srinivasan, 2018).

In addition to the intense inflammation findings due to chemical burns in the cornea, corneal neovascularization may also develop depending on the severity of the damage. This condition may cause permanent damage progressing to blindness. Corneal neovascularization is a process triggered by VEGF. Anti-VEGF agents (e.g., bevacizumab) are known to be effective in the treatment of corneal neovascularization (Chang et al., 2012). In the literature, it was found that Theranekron decreased VEGF expression in colon and liver tissues in a cancer model in rats (Dik et al., 2022). In this study, it is noteworthy that Theranekron decreased VEGF expression in eye tissue. In addition, the lower number of vessels in Groups 3 and 4 compared to Groups 1 and 2, as shown histologically, supports this finding.

Corticosteroids have a dual effect on corneal healing: They can delay epithelialization while suppressing inflammation (Palioura et al., 2016). Since it is used locally, it can cause thinning of the epithelium. It is also known to increase the risk of glaucoma in long-term use (Phulke et al., 2017). Theranekron does not have this disadvantage, making it an alternative treatment. However, considering the success of dexamethasone in systemic applications (e.g., in the treatment of uveitis), combination therapies can be investigated to expand the spectrum of action of Theranekron.

Theranekron has not yet been studied in humans. Structural differences between the human and rat cornea (e.g., stromal thickness) must be considered. In addition, standardization of homeopathic preparations and dose optimization are critical. The study included a 7-day follow-up period. The chronic phase of corneal healing (e.g., scar formation) was not evaluated. Longer-term studies and more detailed analyses may further elucidate these healing effects of Theranekron and perhaps enable its use in clinical studies.

In conclusion, this study demonstrates that Theranekron, a homeopathic preparation derived from Tarantula cubensis venom, has

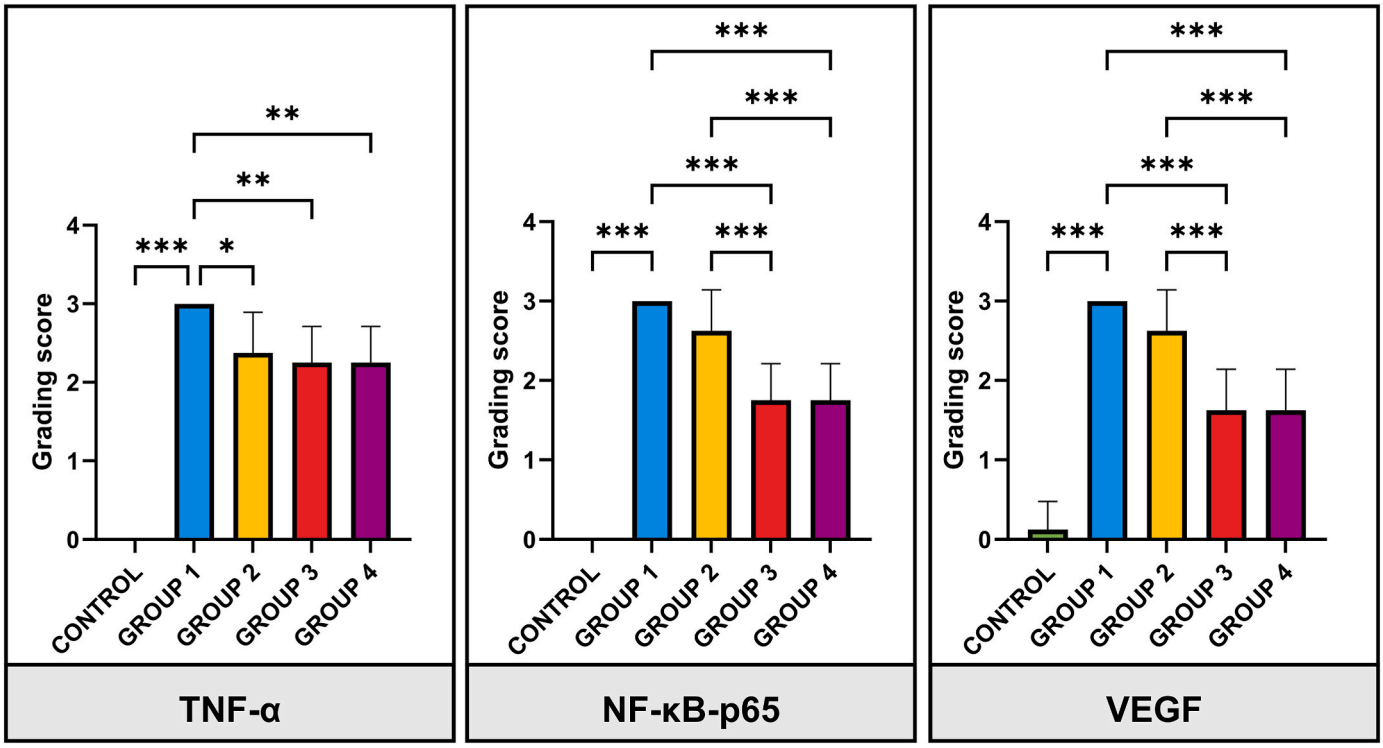


Fig. 4. Immunohistochemical grading scores among groups
TNF-α: Tumor necrosis factor alpha, NF-κB-p65: Nuclear factor kappa-light-chain-enhancer of activated B cells p65, VEGF: Vascular endothelial growth factor. Statistical analysis was performed with one-way ANOVA Tukey test "*" represents $p < 0.05$, "**" represents $p < 0.005$, "***" represents $p \leq 0.001$. Group 1: Damage, Group 2: Damage + Dexamethasone, Group 3: Damage + Theranekron, Group 4: Damage + Sc. Theranekron.

significant potential as a therapeutic agent for corneal injuries. Its ability to reduce inflammation, inhibit neovascularization, and promote tissue repair makes it a promising alternative to conventional treatments such as dexamethasone. While further research is required to confirm these findings in humans, the results of this study provide a solid foundation for future research into the use of Theranekron in ocular medicine.

CRediT authorship contribution statement

N.F. Karakuyu: Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **M.N. Kaya:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **G. Usta Sofu:** Writing – review & editing, Methodology, Investigation, Formal analysis. **E. Sarman:** Writing – review & editing, Visualization, Formal analysis, Data curation.

Consent for publication

Not applicable.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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